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# HMPWG - Questions and Answers on First safe Dilutions

**A. Comparison of the HMPWG publications Q&A on FSD documents**

1-5 (from 12 **November 2013**) and Q&A 6 (from 5 **June 2014**) (**Before** public consultation)

**with**

Q&A document 1-6 (published **October 2015**) (**After** public consultation)

| | Question | Answer (Nov 2013 and June 2014) | Answer (October 2015) |
|---|---|---|---|
| Question 1 | What toxicological data should be submitted in case of an application of a homeopathic medicinal product for oral administration with a dilution equivalent to 12CH or above 12CH? | In case of a dilution equivalent to 12CH or above 12CH, the reference to the present version<br>"Points to consider on non clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin" in Module 4 will suffice.<br>However, the relevant guidelines should still apply for the excipients and the impurities or degradation products detected. | |
| Question 2 | How is the First Safe Dilution elaborated by HMPWG to be applied? | The HMPWG will define one First Safe Dilution for each stock under assessment. This First Safe Dilution can be regarded as safe (referring to a dose of stock that is present in 10 ml of oral solution or in 10 g of trituration) without presenting further data in module 4 and with reference to the FSD list. The definition of a First Safe Dilution does not exclude acceptance of applications for registration of homeopathic medicinal products containing active substances in lower potencies of the stock in question. In such cases applicants should provide adequate data in module 4 and/or calculations referring to the concentration in the finished product in order to justify other potencies. Lower potencies of stocks with appropriate concomitant warnings or contraindications as detailed in the FSD Assessment Report could be acceptable provided that the supportive FSD Assessment Report is integrated in module 4. | |

| | Question | Answer (Nov 2013 and June 2014) | Answer (October 2015) |
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| Question 3 | Should contraindications, in particular allergies, be taken into account when determining the first safe dilution (FSD)? | The approach when determining the FSD should be conservative and only one FSD is applicable per stock. The FSD is the dilution of stock that is safe in all patient groups and so generally contraindications are not relevant. If an applicant wishes to have a lower potency of the stock in their finished product, they must submit a module 4 and address any relevant contraindications on the product labelling.<br>Contraindications with respect to allergies should be established if the allergenic properties of a substance are well-known and should be appropriately addressed on the product labelling. | |
| Question 4 | How is the concept of First Safe Dilutions to be applied to homeopathic medicinal products which are combination products? | Basically the defined First Safe Dilutions can also be applied for combination preparations. Module 4 of the applications should include reflections on possible additive and/or synergistic effects of the different active substances and consequences for calculation of product- specific safe dilutions. | |
| Question 5, paragraph 1 to 5 | What is the background to use the value of TTC 0.15 µg/d? | According to point 3.2 of the "Points to consider on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin" (PtC, July 2007), the TTC value has to be taken as reference for the determination of FSD of genotoxic homeopathic medicinal products (excluding aristolochia species and some structural groups as detailed in point 3.2 of the PtC, see below)<br>"3.2 Background information on TTC principle<br>For genotoxic homeopathic medicinal products of botanical, mineral and chemical origin and under the conditions as defined in Annex 1, the recommendations formulated in the Guideline on the Limits of Genotoxic impurities (CPMP/SWP/5199/02)* are chiefly followed. However, the recommendations by Kroes et al. (2004[2]) with respect to the level of the Threshold of Toxicological Concern (TTC) are applied and therefore a TTC of $0.15.10^{-3}$ mg/day is defined.<br>According to the recommendations by Kroes et al. (2004) the following structural groups were excluded from the TTC approach: aflatoxins, nitroso- and azoxy-compounds, heavy metals, polyhalogenated dibenzodioxin, -dibenzofuran or – | |

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| | Question | Answer (Nov 2013 and June 2014) | Answer (October 2015) |
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| | | biphenyl. Additionally, Aristolochia species are excluded from the TTC approach for homeopathic medicinal products of botanical origin in compliance with the Position Paper on the Risks Associated with the Use of Herbal Products containing Aristolochia species (EMEA/HMPWP/23/00). The TTC approach is not applicable for these substances and consequently the non-clinical risk assessment should be performed on a case-by-case basis and should involve the submission of a module 4."<br>*"Threshold of Toxicological Concern (TTC) is proposed. A TTC value of 1.5 µg/day intake of a genotoxic impurity is considered to be associated with an acceptable risk (excess cancer risk of <1 in 100,000 over a lifetime) for most pharmaceuticals. From this threshold value, a permitted level in the active substance can be calculated based on the expected daily dose. Higher limits may be justified under certain conditions such as short-term exposure periods."(Guideline on the Limits of Genotoxic impurities CPMP/SWP/5199/02).<br>Taking into account the fact that<br>- in the "allopathic field", children will usually get lower quantities of the medicinal product which is not systematically the case in homeopathy,<br>- a benefit risk assessment is not applicable in the context of the simplified procedure and as such safety always prevails<br>- the FSD is considered the most conservative approach which must apply to all patients groups and all treatment durations,<br>it has been decided to set the TTC value at of 0.15µg/d as recommended in the "Points to consider on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin" (July 2007). | |

| | Question | Answer (Nov 2013 and June 2014) | Answer (October 2015) |
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| Question 5, paragraph 6 | (see above) | This TTC threshold is also applied by EFSA, however expressed here on a µg/day basis. With respect to the use of the TTC for the determination of an FSD it is considered that there is no need for further adjustment for body weight taking into account both the conservatism in the TTC approach (0.15 µg/day instead of 1.5 µg/day as recommended in the Guideline on the Limits of Genotoxic impurities CPMP/SWP/5199/02 **and ICH M7**) and the anticipated benefit of the medicinal product. | This TTC threshold is also applied by EFSA, however expressed here on a µg/day basis. With respect to the use of the TTC for the determination of an FSD it is considered that there is no need for further adjustment for body weight taking into account both the conservatism in the TTC approach (0.15 µg/day instead of 1.5 µg/day as recommended in the Guideline on the Limits of Genotoxic impurities [CPMP/SWP/5199/02**] and Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk, M7 [June 2014])** and the anticipated benefit of the medicinal product. |
| Question 6, part 1, paragraph 1 to 3 | Why is a safety factor of 100 introduced when the lowest human recommended dose is used for establishing the FSD? | The factor 100 has its origin in two different contexts:<br>1. Article 14 of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001on the Community code relating to medicinal products for human use states that "…in particular, the medicinal product may not contain either more than one part per 10 000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy with regard to active substances whose presence in an allopathic medicinal product results in the obligation to submit a doctor's prescription."<br>The lowest human recommended dose (LHRD) of a prescription drug may hence be used for the calculation of a first safe dilution (FSD) through division by 100. | |

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| | Question | Answer (Nov 2013 and June 2014) | Answer (October 2015) |
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| Question 6, part 1, last paragraph | (see above) | In the **PtC** it is stated that the LHRD should be applied also for herbal medicinal products, even though the majority of herbals are non-prescription drugs. | In the **Points to consider on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin (PtC, July 2007)** it is stated that the LHRD should be applied also for herbal medicinal products, even though the majority of herbals are non-prescription drugs. |
| Question 6, part 2 | (see above) | 2. The LHRD can also be used to calculate a permitted daily exposure (PDE) by applying it as a LOEL (lowest observed effect level), making the assumption that a recommended dose gives a desired effect.<br>A PDE may then be calculated in accordance with appendix 3 of ICH Q3C (Impurities: Guideline for residual solvents). A number of modifying factors are used (F1-F5), but when a LHRD is used instead of a NOEL or LOEL, only factors F2 and F5 remain, where F2 = 10 to account for variability between individuals and F5 is a variable factor that may be applied if the no-effect level was not established. When only LOEL is available, a factor up to 10 could be used for F5.<br>In calculating the FSD, the most conservative approach is always used, so F5 = 10.<br><br>Taken together, these two modifying factors are equivalent to a factor of 100.<br>The other modifying factors are adjusted as follows:<br>F1 is used for extrapolation between species, but since LHRD and FSD both relate to humans F1 = 1. F3 is used when only short term exposure studies are available.<br>For authorized or registered medicinal products the long term use is studied and used in the benefit risk ratio so F3 = 1. F4 is used only for severe toxicity (nongenotoxic carcinogenicity, neurotoxicity, teratogenicity or reproductive toxicity). | |

| | Question | Answer (Nov 2013 and June 2014) | Answer (October 2015) |
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| | | When LHRD/100 is used, F4 = 1. LHRD/100 is only suitable for non-genotoxic, non-carcinogenic, non-teratogenic material, as stated in Annex 1 of the PtC. If severe toxicity is exerted by the raw material, a more elaborate assessment of the FSD is required.<br>For certain starting materials, a LHRD may have limitations through e.g. known adverse effects, contraindications, special warnings, special patient groups etc. In these cases, a different method for calculation of FSD should be used or the limitation should be taken into consideration when using the LHRD for calculation of an FSD. The decision has to be made on a case by case basis. | |

Remark: Changes are highlighted in **bold**.

Assessment and conclusion:

Only two formal changes have been made to the answers on question 5 and 6.

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**B. Comparing the outcome of the HMPWG to the comments of ECHAMP, AESGP and ECH given on the (draft) Q&A documents 1-5 and 6 (Nov 13 and June 14)**

Remarks

Where useful the essence of the comment is given and/or the outcome is summarised; sometimes the whole comment or outcome is repeated.

For better understanding and structure comments from each party have been numbered.

**B.1** Overview of comments received and outcome given by the HMPWG adopted in May 2015 **(Q&A 1-5)**

| Q&A No. | Comment / Question | Outcome HMPWG |
|---|---|---|
| **General** | Question from Lab. Lehning | Not endorsed |
| | Question from Lab. Lehning | Not endorsed |
| | Question from Lab. Lehning | Not endorsed |
| **1 and 2** | - | - |
| **3** | Comment from ECHAMP | Not endorsed |
| | Comment from AESGP | Not endorsed |
| **4** | Comment from ECH | Not endorsed |
| | Question from Lab. Lehning | Question answered |
| **5 ECHAMP** | Comment 1 from ECHAMP (pages 5+6 of the document "Overview of comments …")<br>**We therefore request that a TTC of 1.5 µg/day is likewise accepted for genotoxic homeopathic medicinal products**. | Not endorsed:<br>The HMPWG refers to question 5 [answer] (1) - (3) and the "GUIDELINE ON THE ASSESSMENT OF GENOTOXICITY OF HERBAL SUBSTANCES/PREPARATIONS, chiefly. "Availability of data and particulars of different treatment concept have to be taken into account.<br>There are a lot of very specific ways (Anthropos., biochemical) of using hom. remedies and they are used by therapist as well as in self- |

| Q&A No. | Comment / Question | Outcome HMPWG |
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| | | medication Therefore a dosage of 10 mL is possible as well as an intake over a longer period even lifetime.<br>Disclaiming of a body weight adjustment is balancing the difference.<br>It is possible to apply for a lower dilution e.g. with AMES test and an assessment in CTD Module 4. |
| | Comment 2 from ECHAMP (page 6)<br>**We therefore request that a TTC of at least 1.5 µg/day is accepted for homeopathic substances without genotoxic potential for which a PDE cannot be derived.** | [Not endorsed:]<br>It is not correct that the TTC factor in Annex 1 is required for "substances **without** genotoxic potential" but for "substances **with unknown** genotoxic potential"<br>No inconsistency in terms of a higher PDE than TTC value (TTC concept is used, if only very little information available about the substance, PDE is merely possible on the basis of valid studies).<br>[Remark: ECHAMP comment on EFSA concept is not answered.] |
| | Further comments (3 - 5) from ECHAMP (pages 7 and 8) (plea and closing words):<br>[3] Multiplication of safety factors<br>[4] Some member states allow a posology or amounts of daily intake for different age groups for HMPs registered acc. to Art. 14<br>[5] Welcome of personal exchange and discussion | [3] no answer to the comment is given<br>[4] "Suitable packaging information in terms of dosage are not required for article 14 medicinal products. For these medicinal products 10 mL must be safe."<br>[5] no answer to the comment is given |
| **5**<br>**ECH** | Comment 1 from ECH (page 9)<br>We propose a conservative pragmatic default threshold value of 1.5 µg/day in the safety assessment of complex homoeopathic mother tinctures. | Not endorsed:<br>answer complies with the one given to the ECHAMP (to comment 1). |

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| | Comment 2 from ECH (page 9)<br>Nobody intakes 10 ml of dilution or 10 g of trituration every day! These are exceptions, for instance in cases of accidental overdoses. | … there are a lot of very specific ways (anthroposopical, biochemical, etc) of using homeopathic remedies. They are used by therapist as well as in self-medication. Therefore for example the dosage of 10ml isn`t necessarily a theoretically one. And an intake over a longer period or even lifetime isn`t unthinkable. …*[see also answer to comment 1 to ECHAMP]*. |
| | Comment 3 from ECH (page 10)<br>The TTC concept is aimed at providing a tool for the risk assessment of defined chemical structures (such genotoxic impurities). It is a wrong scientific basis to apply it for ill-defined homeopathic preparations. | Using the TTC concept is a pragmatical toxicological approach to assess substances for which neither analytical (chemical or phytochemical) nor toxicological data are available. If there is knowledge available about the substance other approaches are used, e.g. PDE or the TTC-value can be applied on the relevant toxicological principle of a mixture if the content of it has been determined using a validated method. |
| | Comment 4 from ECH (page 10)<br>EFSA does not consider the use of the TTC concept for ill-defined mixtures, as HMA does. | *[No answer to the comment is given, but outcome is given later to AESGP comment 5]* |
| | Comment 5 from ECH (page 10)<br>The notion that ”in the allopathic field, children will usually get lower quantities of the medicinal product which is not systematically the case in homeopathy” is not correct. E.g. the German Com D foresees the dosage to be proportional to the age groups. … | Commission D is a national committee and has no validity in the EU. |
| | Comment 6 from ECH (page 10)<br>The wording ‘genotoxic homeopathic medicinal product’ as used in the answer, is scientifically unacceptable. In particular that any homeopathic preparation substantially consists of constituents like water and ethanol which are acknowledged to be non-genotoxic. | We agree to use the wording “homeopathic medicinal product including a substance with genotoxic potential” instead of ‘genotoxic homeopathic medicinal product’ |

| Q&A No. | Comment / Question | Outcome HMPWG |
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| **5**<br>**AESGP** | Comment from AESGP<br>1. Background information on TTC principle ("3.2") (pages 11 - 13)<br>According to Kroes et al (2004), the numerical limit value of 0.15 x 10-3 mg/day shall only apply if structural alerts are apparent. …<br>Kroes uses a decision tree. The decision tree has been developed in order of decreasing concern, beginning to eliminate those compounds from the decision tree at an early stage which belong to the Cohort of Concern (CoC) and therefore a TTC determination is considered inappropriate….<br>The decision tree only leads to 0.15 x 10-3 mg/day if the question "Are there alerts that raise concern for potential genotoxicity" is to be answered with YES. Otherwise 1.5 x 10-3 mg/day applies. Later in the decision tree, adverse effects that would show a threshold in the dose response curve are addressed lead to higher numerical values. Concerning chemicals or herbals for which no or only few data is available, but which do not have structural alerts, the HMA's approach leads to an unjustified discrimination. This is shown by a tabulated comparison of the different standards and regulations in Table 1 Regulatory framework, see below. [*Remark: Table 1 "Regulatory framework" has not been included in this HMA comment paper*]<br>The typical field of application of this concept is the occurrence of minor contaminants or residues in food, cosmetics, food, additives etc. Recently, the concept has also been applied to the issue of impurities in medicinal drugs (Müller et al., 2006).<br>The use of the same concept to evaluate the risk related to the consumption/intake of an ill-defined mixture of many, even hundreds of components, is unscientific. It means a misuse of the concept and contradicts the major ideas and aims of TTC. | 1. Background information on TTC principle ("3.2")<br>Not endorsed: According to Annex 1 of the "PtC on Nonclinical Safety of Homeopathic Medicinal Products of botanical, mineral and chemical origin", TTC should only be applied if there is a sufficient phytochemical or chemical characterization provided for a starting material, otherwise the FSD will be CH12. |

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| | Comment from AESGP: 2. Comparison with allopathic medicines (pages 13 - 14)<br>The notion is made that “in the allopathic field, children will usually get lower quantities of the medicinal product which is not systematically the case in homeopathy.”<br>From our point of view this is not correct. E.g. in Germany the Advisory Board for Homeopathy (Commission D)* issues a dosage for each homeopathic medicine stipulating that the dosage is to be proportional to the age groups. Therefore the dosage is adapted to the age and reduced in younger patient. | 2. Comparison with allopathic medicines<br>Not endorsed: There is no dosage required for Article 14 medicinal product. Besides the dosage recommendation of the Commission D is a national one and not binding in the EU |
| | Comment from AESGP: 3. Considerations on the simplified procedure (page 14)<br>The text states that "a benefit risk assessment is not applicable in the context of the simplified procedure and as such safety always prevails".<br>We understand that the FSD principle is to allow marketing of a product without producing particular evidence and discussion on the safety of the individual ingredients of the medicinal products as long as each ingredient is present in amount below the FSD. This very conservative approach setting the TTC value 10 times lower than for pharmaceuticals in general seems to be justified by this lack of evidence. However, according to this Q&A, this approach does not apply to marketing authorisation of homeopathic products according to Art. 16 of the European Directive. | 3. Considerations on the simplified procedure<br>[No answer is given to the comment.] |
| | Comment from AESGP: 4. FSD as most conservative approach (page 14 - 15)<br>The Q&A document states that “… the FSD is considered the most conservative approach which must apply to all patients groups and all treatment durations”.<br>We would like to refer to the Expert statement of Prof. Schrenk (2014) [5] explaining the following:<br>“Even under the simplistic consideration of an extreme precautionary principle and despite the wrong scientific basis of the above mentioned approach, it is a | 4. FSD as most conservative approach<br>Partly agreed: instead of the wording “genotoxic homeopathic medicinal product” “homeopathic medicinal product including a substance with genotoxic potential” is appropriate.<br>In case of a valid description of the genotoxic component of the substance the calculation was executed with the single component. If there wasn`t valid information available about the component, as a |

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| | matter of fact that any homeopathic preparation substantially consists of constituents like water and ethanol which are acknowledged to be non-genotoxic. Since these are well known to represent the major part of the mother tincture (a D2 homeopathic preparation consists, e.g. of at maximum 0.01 g substance, and at least 0.99 g water/ethanol mixture) in most preparations, it appears severely over-conservative to assume that water, ethanol etc. should be considered as genotoxic carcinogens. Furthermore, there is no practical need for such an approach since the contents of innocuous solvents in the mother tincture are well known. The wording 'genotoxic homeopathic medicinal product' as used in the answer is scientifically unacceptable.<br>With respect to treatment duration, the TTC concept has been established for lifetime exposure, which is not feasible for most types of medication including use of homeopathic medication. Alternatives using less-than-lifetime corrections as published by Müller et al. (2006) for drug impurities are discussed in the literature." | pragmatical approach the whole amount of the starting material was taken.<br><br>[*Remark: No answer/comment is given to the last paragraph.]* |
| | Comment from AESGP: 5. Application of the TTC threshold by EFSA (pages 15 - 16) *(similar is ECH comment 4 on Q&A 6, General)*<br>The Q&A states that "This TTC threshold is also applied by EFSA, however expressed here on a µg/day basis".<br>According to the Expert statement [Encl. 1] *[Remark: "Encl. 1" has not been included in this HMA comment paper]* the following should be taken into account:<br>"The statement suggests that EFSA considers the use of the TTC concept for ill-defined mixtures as HMA does. This notion is incorrect. The 'Scientific Opinion on exploring options for providing advice about possible human health risks based | 5. Application of the TTC threshold by EFSA<br>Partially agreed: According to Annex 1 of the "PtC on Non-clinical Safety of Homeopathic Medicinal Products of botanical, mineral and chemical origin", TTC should only be applied if there is a sufficient phytochemical or chemical characterization provided for a starting material, otherwise the FSD will be CH12. |

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| | on the concept of Threshold of Toxicological Concern (TTC)' states under 4.4.3.3. 'Mixtures': 'It is possible to apply the TTC approach to mixtures containing only substances with closely related chemical structures, but then dose addition should be assumed and the exposures should be summed. However, there has been little evaluation of the applicability of the TTC approach to mixtures containing substances of unknown structure. Accordingly, such mixtures should be excluded from the TTC approach' (EFSA, 2012). Therefore, if the TTC threshold is applied, it should be used as in the safety assessment of contaminants in food or in the field of genotoxic impurities in pharmaceuticals. The TTC threshold should be applied to single components within the homeopathic mother tincture and not to complete mixture of many different structures. | |
| | Comment from AESGP: 6. Adjustment of body weight (page 16 - 17) *(partly also in ECH comment 6 on Q&A 6, General)*<br>We do appreciate that the benefit of the homeopathic medicinal products is positively highlighted in this context. Nevertheless we do not agree to the assumption that due to a lower TTC no body weight adjustment is necessary, for the following reasons:<br>1) The TTC concept is based on the daily exposure in an adult of 60 kg.<br>2) The body weight adjustment of a safety threshold is common scientific practice in toxicology. It is scientifically not comprehensible to use one threshold without body weight adjustment.<br>3) The dosage of many homeopathic medicinal products is recommended according to the age group and body weight, implying a lower exposure in smaller patient.<br>4) Due to the specific manufacturing preparation of homeopathic remedies supplementary dilution factors are already included. | 6. Adjustment of body weight<br>Not endorsed. AESGP recommends TTC value of 1.5µg/day with body weight adjustment. As the FSD has to be valid for all patient groups, it has to be calculated for a new-born infant (1.5 µg ÷ 60 kg x 3 kg = 0,075 µg/day).This calculation would lead to a more conservative value as using TTC 0.15 µg without body weight adjustment.<br>There are no dosage recommendations foreseen for registered homeopathic medicinal products. |

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| | As a consequence the TTC approach including a supplementary safety factor of 10 and being more conservative for homeopathic medicinal products as compared to other medicinal products is not necessary and not justified. | |
| | Comment from AESGP: 7. Conclusion (pages 17 - 18)<br>Complex mixtures of substances can be found in homeopathic mother tinctures and thus in homeopathic medicinal products. A reasonable and pragmatic scientific approach for the risk assessment of a potential genotoxicity would be is to consider a default threshold value and not the TTC concept.<br>…<br>For the reasons discussed above, we propose to use a conservative pragmatic default threshold value of 1.5 µg/day in the safety assessment of complex homeopathic mother tinctures.<br>The following Table (Table 2) [*Remark: Table 2 has not been included in this HMA comment paper*] shows which limits have been set within the regulatory framework based on the consideration of an accepted risk, see below. | - |

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**B.2** Overview of comments received and outcome given by the HMPWG adopted in June 2015 **(Q&A 6)**

| Q&A No. | Comment / Question | Outcome HMPWG |
|---|---|---|
| **General**<br>**AESGP** | Comment 1 from AESGP:<br>We would like to express our concerns that calculations from safety assessments of non-homeopathic medicines are transposed to homeopathic medicinal products. This results in an increasing limitation of safe dilutions beyond or far beyond D4. We therefore strongly plead for taking sufficiently into account the particularities of homeopathic medicinal products, in particular the safety criterion of D4 laid down in Directive 2001/83/EC as well as the fact that homeopathic preparations of D4 and above did not show any relevant safety problems during their long presence in the market. | Not endorsed.<br>D4 cannot be regarded as safe for all stocks that are used in homeopathy; if this would be the fact, the assessment to establish FSDs would not be necessary. That non homeopathic medicines can only be used in homeopathy after applying a safety margin (Article 14 2001/83/EC: 1/100th of the smallest dose used in allopathy) implicates, that the safety assessment of allopathics is even not sufficient for homeopathic medicinal products. From missing reports of adverse events cannot be concluded that homeopathic medicinal products are safe, because both physicians and patients perceive homeopathic medicinal products as harmless and even for non-homeopathic medicines an underreporting of adverse events is documented (Lorna Hazell and Saad A.W. Shakir: Under-Reporting of Adverse Drug Reactions. A Systematic Review; Drug Safety 2006; 29 (5): 385-396). |
| | Comment 2 from AESGP (*similar to comment 1 ECH and comment 2 ECHAMP, see below)*:<br>We consider it unacceptable to have one FSD per stock (as for Atropa and Chimaphila). The safety, i.e. the FSD, has to be determined in relation to the manufacturing method, as the amount of toxicologically relevant substances in fact depends on the manufacturing method.<br>Therefore, the FSD can differ with the manufacturing method. For example, for Chimaphila, the calculation of FSD gives D8 for method | Not endorsed.<br>The FSD shall represent the most conservative approach of the toxicological assessment. If an applicant claims a lower potency for a stock than determined in the list entry, he must submit a Module 4. |

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| | 1.1.5, and D7 for method 1.1.10. We therefore suggest, as proposed earlier, to have different FSDs taking into account the manufacturing method and to include the different manufacturing methods in the same assessment report. | |
| | Comment 3 from AESGP *(complies with comment 4 from ECHAMP)*:<br>We cannot understand why it is no longer possible to give a FSD for adults with warnings, and one for all user groups without warnings (see also comments submitted in 2012). | Not endorsed.<br>The FSD shall represent the most conservative approach of the toxicological assessment. According to Question 3 of the Question and Answer document the FSD should be safe for all patient groups. If an applicant claims a lower potency for a stock than determined in the list entry, he must submit a Module 4. |
| | Comment 4 from AESGP:<br>Inclusion of a reference list at the end of the respective assessment report would be useful in order to have a detailed look into the toxicological data quoted. | Accepted.<br>The toxicological assessment should be replicable. |
| | Comment 5 from AESGP:<br>As a general remark we would like to suggest that the documents on FSD and Q&A are available permanently on the HMA website, and not only during the consultation phase. Moreover, we would appreciate if the Q&As were provided on the HMA website as consolidated whole version and not only the Q&A under consultation. | Accepted.<br>Guidance documents should be available without limitations. |
| **General ECH** | [*Comment complies with comment 2 from AESGP and is therefore not repeated here]* | *[The outcome is identical with the one given to the AESGP - please see above]* |

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| | Comment 2 from ECH [*complies with comment 7 of AESGP on Q&A No 5, see above*]:<br>… Complex mixtures of substances can be found in homoeopathic mother tinctures and thus in homoeopathic medicinal products. A more reasonable and pragmatic scientific approach for the risk assessment of a potential genotoxicity would be is to consider a default threshold value and not the TTC concept. | *[No answer or comment is given]* |
| | Comment 3 from ECH [*complies with comment 1 of AESGP on Q&A No 5, see above]*:<br>The direct application of the "TTC for genotoxic substances with known genotoxic alerts" of i.e. 0.15 µg/day to the complete complex mixture is scientifically not justified. This assumption is, also in a "worst case scenario", not justified. | Partially accepted.<br>The TTC-value can be applied on the relevant toxicological principle of a mixture if the content of it has been determined using a validated method.<br>For HMPWG internal only:<br>→ Minutes FSD subgroup meeting 20130307, TOP 4.3: "Belgium could agree to calculate the FSD via TTC based on the content of the relevant toxicological compound / compound group only if sufficient data (based on validated analytical methods) are available, covering all toxic components of the plant material." This statement was not considered in the Q&A Document. |
| | Comment 4 from ECH [*complies with comment 5 of AESGP on Q&A No 5, see above]*:<br>If the TTC is applied, it should be used as in the safety assessment of contaminants in food or in the field of genotoxic impurities in pharmaceuticals. | Not endorsed.<br>Availability of data and particulars of different treatment concept have to be taken into account. For application of the TTC principle in food see EFSA Journal 2012;10(7):2750. The EFSA Scientific Committee recommends TTC 0,15 µg for assessing substances with a structural alert for genotoxicity in food. |

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| | Comment 5 from ECH [*complies with last sentence of comment 5 of AESGP on Q&A No 5, see above]*:<br>The TTC should only be applied to single components within the homoeopathic mother tincture and not to a complete mixture of many different structures including water and ethanol. | Partially accepted, see above.<br>TTC will be applied on the content of the starting material in the mother tincture or, if there are sufficient data, on the relevant toxicological principle of a mixture if the content of it has been determined using a validated method. |
| | Comment 6 from ECH [*complies with comment 6 of AESGP on Q&A No 5, see above]*:<br>The dosage for children is adapted to age and body weight in many homoeopathic products. In case the TTC concept is applied, this aspect reinforces the idea that no supplementary safety factor of 10 has to be applied and the TTC of 1.5 µg/day is valid. | Not endorsed.<br>According to the "Points of consider on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin" the FSD should be calculated for 10 ml of oral solution or 10 g trituration. As not all homeopathic medicinal products will be placed on the market with a dosage recommendation for adults or children, a supplementary safety factor of 10 cannot be expected in general. |
| | Comment 7 from ECH:<br>Homoeopathic medicinal products are not taken daily over the whole life. This aspect has to be taken into consideration when applying safety thresholds (staged TTC approach). | Not endorsed.<br>The simplified registration procedure for Homeopathic Medicinal Products with referring to the list of FSD is a special offer to the applicants. If they want to deviate from the framework regulating this procedure, they have the possibility to provide additional data. |
| | Comment 8 from ECH [*complies with comment 6 of ECH on Q&A No 5, see above]*: The homoeopathic mother tincture or the homoeopathic medicinal product cannot be equated to a "genotoxic homoeopathic medicinal product". | Accepted. We agree to use the wording "homeopathic medicinal product including a substance with genotoxic potential" instead of 'genotoxic homeopathic medicinal product'. |
| | Comment 9 from ECH *[= conclusion]*: | Not endorsed. |

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| | For the reasons discussed above, we propose to use a conservative pragmatic default threshold value of 1.5 µg/day in the safety assessment of homoeopathic mother tinctures or other starting materials. | The applicant always has the possibility to submit additional data to get a lower potency than determined in the FSD. |
| **General ECHAMP** | Comment 1 from ECHAMP:<br>The present examples show that due to the specificity of the calculation sources and safety factors the original intention of the FSD list to simplify the dossier workload and assessment for registration applicants and agencies cannot be met.<br>In practice, the applicants need to submit own Modules 4 in order to prove the safety of their potency ranges. | *[No comment is given.]* |
| | Comment 2 from ECHAMP:<br>In the comments submitted in 2012 we proposed to have one assessment report for one plant, including the different manufacturing methods in the same report. HMPWG did not follow this proposal for Atropa belladonna, since there is one Assessment report for method 1.1.3 (Ph. Eur) and another one for method 21 (GHP).<br>-> **we still suggest to include the different manufacturing methods in the same Assessment report.** | Accepted. |
| | Comment 3 from ECHAMP *[complies with comment 2 of AESGP and comment 1 ECH]:*<br>Concerning the evaluation of the safety we consider it unacceptable to have one FSD per stock (as for Chimaphila). The safety, i.e. the FSD, has to be determined in relation to the manufacturing method, | Not endorsed.<br>The FSD shall represent the most conservative approach of the toxicological assessment. If an applicant claims a lower potency for a stock than determined in the list entry, he must submit a Module 4. |

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| | as the amount of toxicologically relevant substances in fact depends on the manufacturing method.<br>-> **we likewise suggest to state different FSDs if they exist taking into account the manufacturing method**. | |
| | Comment 4 from ECHAMP *[complies with comment 3 of AESGP]*:<br>Furthermore, we cannot understand why HMPWG did not further endorse to give a FSD for adults with warnings, and one for all user groups without warnings, especially as this was in fact a proposal of the HMPWG which was explicitly welcomed by AESGP and ECHAMP (see comments submitted in 2012).<br>-> **we propose to keep the possibility to state a FSD for adults (if applicable with warnings) and a FSD for all user groups in the list entry, and not only in the assessment report.** | Not endorsed.<br>The FSD shall represent the most conservative approach of the toxicological assessment. According to Question 3 of the Question and Answer document the FSD should be safe for all patient groups. |
| | Comment 5 from ECHAMP:<br>For the calculation of FSD, we do neither consider it necessary nor feasible to use the TTC approach, when, in accordance with the decision tree of the PtC, another criterion is applicable (as for Atropa belladonna, Atropinum sulfuricum). The HMPWG decision tree in the "Points to consider on non-clinical safety of homeopathic medicinal products of botanical, mineral and chemical origin" on the criteria for the establishment of a FSD allows only "yes" or "no" –answers. It is not foreseen to end up with two criteria. In addition, the TTC is only to be applied when toxicity data are unavailable, or when the respective substance is identified as a genotoxicant. | Partially accepted.<br>If there are only data for a subset of the intended patient group that may receive a homeopathic medicinal product (e. g. dosage recommendations for adults only), it can be necessary to choose a second way of toxicological assessment. The comparison of two approaches as it was practised in the assessment of Atropa belladonna strengthens the "validity" of a FSD, when the two ways of assessment lead to the same result. |

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| | -> **we suggest to follow the decision tree in Annex 1 of the HMPWG document "Points to consider on non-clinical safety of homeopathic medicinal products of botanical., mineral and chemical origin" which means that the TTC concept is not applicable when there is a LHRD**. | |
| | Comment 6 from ECHAMP:<br>Reference for LHRD: Can the standard manual "Normdosen gebräuchlicher Arzneistoffe und Drogen" see Annex 1 [*Remark: Annex 1 has not been included in this HMA comment paper*]) be considered as a valid reference for LHRD? | Partially accepted.<br>The actuality of the data of this standard manual with regard to information to Complementary and Alternative Medicines has to be proven. To define the LHRD, a research is necessary including different sources (monographs, standard manuals, ...). |
| | Comment 7 from ECHAMP*:*<br>As a general remark we would like to suggest that the documents on FSD and Q&A are available permanently on the HMA website, and not only during the consultation period. | Accepted.<br>Guidance documents should be available without limitations. |
| **6 ECHAMP** | General comment from ECHAMP:<br>We do not agree with the argumentation given by HMPWG for the general introduction of factor 100 when LHRD is used for the reasons given below. | *[No comment is given.]* |
| | 1. comment on Answer 1 from ECHAMP:<br>We propose to change or delete the first argument of the HMPWG as – in our opinion, it could be misleading. … | Not endorsed.<br>The first argument of HMPWG corresponds to the statement as given in Article 14 of 2001/83/EC and just describes one possibility of assessment. The approach to applicate a factor of 100 to a substance used in allopathy was extended in the PtC to non-prescription drugs (herbals) as well. |

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| | 1. comment on Answer 2 from ECHAMP:<br>…..<br>We therefore think that the HMPWG answer 1 does not give a satisfying explanation on the general application of the safety factor 100 for LHRD. | Not endorsed.<br>Non-prescription drugs often have a safety profile that does not allow the administration in all patient groups which is reflected in contraindications and special warnings. This circumstance justifies the use of safety factors as the FSD should be safe for everybody. |
| | Comment on Answer 2 from ECHAMP:<br>We do not accept the linking between LHRD and PDE and in this context a general requirement of an additional safety factor 100 for LHRD as such. …<br>Moreover, it is not comprehensible why a recommended single dose including an additional safety factor of 100 is used for the calculation of the PDE as permitted daily exposure.<br>**We therefore think that the HMPWG answer 2 does not give a satisfying explanation on the general application of the safety factor 100 for LHRD.** | Not endorsed.<br>A pharmacological effect of homeopathic medicinal products does not correspond to the principles of homeopathy, therefore the application of F5=10 with regarding the therapeutic dosage of an allopathic medicinal product as a LOAL is justified.<br>In "3.4 Calculation of the first safe dilution" of the PtC the LHRD is defined as mg/day. This approach is not applicable in every assessment because of differing doses recommendations (e.g. pharmaceuticals that are used in single doses only, like Atropine in anaesthesia). The alternative would be to choose a different approach according to the possibilities given in the PtC to assess such substances. |
| | General from ECHAMP:<br>The original aim of FSD calculations was the avoidance of the submission of individual Modules 4. This aim cannot be met for most homeopathic stocks by using the concept proposed by HMPWG. | Not endorsed.<br>It is the aim of HMPWG to provide FSDs that are safe for all patient groups. If an applicant claims a lower potency, he has to discuss the safety issues in module 4. |